Reviews

Renal Effects of Environmental and Occupational Lead Exposure

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Environmental and industrial lead exposures continue to pose major public health problems in children and in adults. Acute exposure to high concentrations of lead can result in proximal tubular damage with characteristic histologic features and manifested by glycosuria and aminoaciduria. Chronic occupational exposure to lead, or consumption of illicit alcohol adulterated with lead, has also been linked to a high incidence of renal dysfunction, which is characterized by glomerular and tubulointerstitial changes resulting in chronic renal failure, hypertension, hyperuricemia, and gout. A high incidence of nephropathy was reported during the early part of this century from Queensland, Australia, in persons with a history of childhood lead poisoning. No such sequela has been found in studies of three cohorts of lead-poisoned children from the United States. Studies in individuals with low-level lead exposure have shown a correlation between blood lead levels and serum creatinine or creatinine clearance. Chronic low-level exposure to lead is also associated with increased urinary excretion of low molecular weight proteins and lysosomal enzymes. The relationship between renal dysfunction detected by these sensitive tests and the future development of chronic renal disease remains uncertain. Epidemiologic studies have shown an association between blood lead levels and blood pressure, and hypertension is a cardinal feature of lead nephropathy. Evidence for increased body lead burden is a prerequisite for the diagnosis of lead nephropathy. Blood lead levels are a poor indicator of body lead burden and reflect recent exposure. The EDTA lead mobilization test has been used extensively in the past to assess body lead burden. It is now replaced by the less invasive *in vivo* X-ray fluorescence for determination of bone lead content. *Key words:* *N*-acetyl β-D-glucosaminidase, gout, heavy metals, hypertension, kidney, nephropathy.

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Lead is one of the most useful elements in industry but serves no useful function in the human body (*1*). Over the past 20 years, it has become increasingly evident that low-level lead exposure resulting in blood lead levels between 10 and 15 µg/dl (0.48–0.72 µmol/l) can lead to deleterious effects, particularly in infants and young children (*2*). The effects of chronic lead exposure include cognitive and behavioral deficits (*3,4*), high blood pressure, and impaired renal function. Since the late 1970s, there has been a substantial reduction or elimination of environmental sources of lead, including house paint, gasoline, water distribution systems, and lead-soldered food and soft drink cans (*4*). Pirkle et al. (*5*) used the data from the National Health and Nutrition Examination Surveys II and III and found that, between 1976 and 1991, the mean blood lead levels for the U.S. population declined from 12.8 to 2.8 µg/dl (0.61–0.13 µmol/l). As a result, the acceptable blood lead levels, also referred to as threshold for action, have been reduced over the years from ≤25 µg/dl (1.21 µmol/l) in 1985 to ≤10 µg/dl (0.48 µmol/l) in 1991, but even the currently accepted blood lead level of ≤10 µg/dl (0.48 µmol/l) may be excessive (*6*).

The purpose of this review is to summarize the current knowledge of the renal effects of chronic lead exposure in humans. Following a review of nephropathy due to occupational lead exposure, I shall discuss the evidence for lead nephropathy following environmental lead exposure in childhood. Other commonly observed symptoms of chronic lead toxicity, including hypertension, hyperuricemia, and gout will also be discussed. I shall conclude with a discussion of the currently available laboratory tests for the determination of body lead burden as well as for evaluation of renal tubular effects of lead.

Historical Aspects

Plumbism, or lead poisoning, has been recognized for many centuries and is one of the oldest ailments afflicting humans. Nikander (200 B.C.) was first to describe the symptoms of lead poisoning, which included colic and pallor (*7*). The English aristocracy of the 17th and 18th centuries suffered from widespread lead poisoning from consumption of Portuguese wine, transported with submerged lead bars to enhance flavor and to prevent spoilage (*8*). Lancereaux (1882) provided the first description of kidney disease and interstitial nephritis by postmortem examination of a lead poisoned artist. Olivier (*9*) also reported on kidney disease in lead poisoning, but failed to differentiate interstitial from glomerular disease (*7*). It was not until the late 1920s when an epidemic of chronic nephritis in Queensland, Australia, was linked to childhood lead poisoning that the full spectrum of lead-induced nephropathy became apparent (*10–12*). This was followed by reports of renal disease from the Southeastern United States in individuals consuming lead-contaminated illegally distilled (moonshine) whiskey (*13*) and in industrial lead workers (*14*).

Environmental Lead Exposure

Although many industrial sources of lead have been eliminated, excessive environmental lead exposure continues to be a public health problem. Seventy to 99% of all houses built prior to 1959 have painted surfaces containing significant amounts of lead (*15,16*). Older housing is also more likely to contain lead plumbing (*17*). In the past, lead-based paint was a major source of lead poisoning in children; however, direct ingestion of lead paint is now a much less common occurrence. Ingestion of lead-contaminated dust and water by children has been

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identified as a major contributor to lead poisoning (*15*). In a recent survey of the District of Columbia, high concentrations of lead were found in soil samples from inner-city areas, and lead-based paint was found to be the main source of lead in soil dust (*18*). That lead-contaminated dust is a major determinant of lead concentrations in blood has been confirmed by studies showing a direct relationship between blood lead levels and lead concentrations in the ground (*19*). Campbell et al. (*20*) found a highly significant correlation between lead concentrations in drinking water and blood lead concentrations in 293 people living in Scotland where the water lead levels were >100 µg/l (4.83 µmol/l). An important current public health concern is continuing high blood lead levels in children and the means to reduce them (*15*). Children are more susceptible to the effects of environmental lead than adults because of increased gastrointestinal absorption of lead in children (*21*). Adults at highest risk are those exposed to lead fumes or dust in industry (*22,23*).

Lead Nephropathy

An association between lead poisoning and renal disease in humans has been recognized for over a century (*8,12,24*). The major renal effect of acute lead poisoning is disruption of proximal tubular architecture, with laboratory evidence of disturbances in proximal tubular function (*25–28*) (Fig. 1). Histologic changes include eosinophilic intranuclear inclusions in proximal tubular cells consisting of lead–protein complexes, and mitochondrial swelling (*29–33*). Renal manifestations of acute lead poisoning have been well described both in animal models and in humans; these include glycosuria, aminoaciduria (*34,35*), and phosphaturia, collectively representing the Fanconi syndrome (*36–38*). These functional changes are thought to be related to an effect of lead on mitochondrial respiration and phosphorylation (*26*). Recent studies have shown that lead can directly inhibit the function of rBAT, a protein involved in the high affinity transport of neutral and dibasic amino acids across renal and intestinal brush borders (*39*). Because lead is also capable of reducing 1,25-dihydroxyvitamin D synthesis (*40*), prolonged hyperphosphaturia and hypophosphatemia caused by lead poisoning in children could result in bone demineralization and rickets (*36*). The renal manifestations of acute lead poisoning are usually reversible after chelation therapy and cessation of lead exposure (*26,37*).

In experimental animals, exposure to high concentrations of lead results in increased glomerular filtration (hyperfiltration) after 3 months of exposure. This is followed by a progressive decline in the glomerular filtration rate (GFR) and irreversible renal failure by 12 months (*41–43*). A blood lead level of 60 µg/dl (2.89 µmol/l) appears to be the threshold for proximal tubular injury in both animal and human studies.

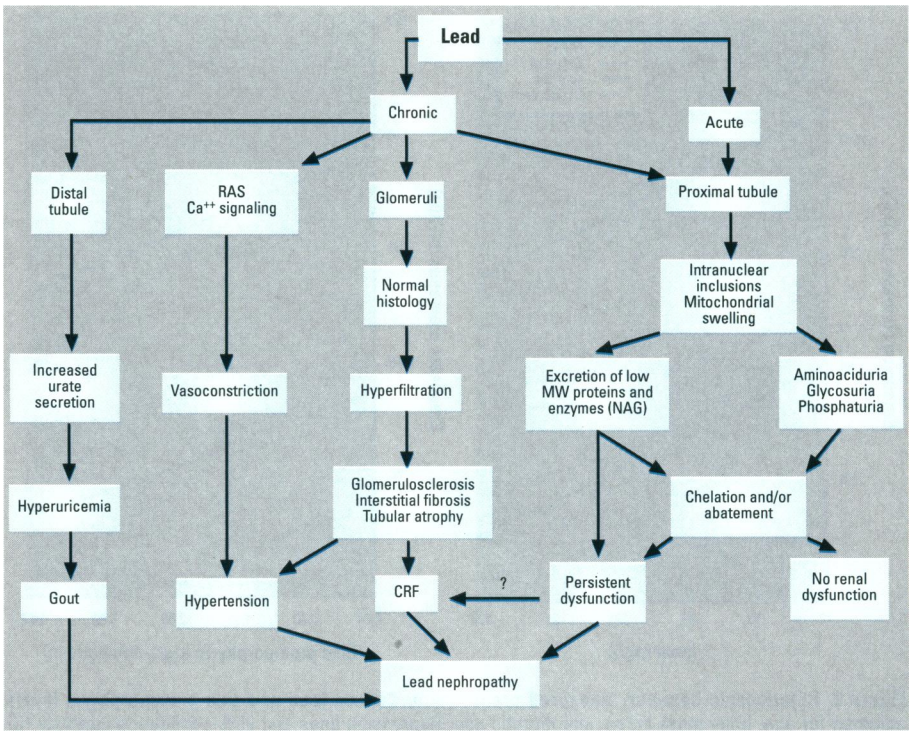

Figure 1. Consequences of excessive lead exposure. Abbreviations: MW, molecular weight; CRF, chronic renal failure; NAG, *N*-acetyl-β-D-glucosaminidase. Acute lead poisoning results in proximal tubular dysfunction; these changes usually disappear with chelation therapy or removal from lead sources. Chronic lead poisoning can affect glomerular function when blood lead levels exceed 60 µg/dl. After an initial period of hyperfiltration, the glomerular filtration is reduced and nephrosclerosis and chronic renal failure ensue. Prolonged lead exposure also interferes with distal tubular secretion of urate, leading to hyperuricemia and gout. Finally, chronic lead exposure may cause hypertension, resulting from vasoconstriction due to the action of lead on the renin–angiotensin system (RAS) and on calcium signaling.

In humans, the symptoms resulting from chronic lead poisoning are subtle, and often the patients remain asymptomatic until significant reductions of renal function have occurred. As in experimental animals, chronic exposure to high levels of lead results in irreversible changes in the kidney, including interstitial fibrosis, tubular atrophy, glomerular sclerosis, and ultimately renal failure, which necessitates replacement therapy (*26,28*) (Fig. 1). These changes are nonspecific and common to many other types of renal injury; therefore, increased lead burden must be ascertained and other causes of renal failure ruled out before making a diagnosis of lead nephropathy. Chronic high-dose lead exposure has also been implicated in the development of gout and hypertension (*13,44*).

Whether chronic lead nephropathy exists as a clinical entity has been questioned (*45*). Many studies of occupational lead poisoning have not taken into account the coexposure to other toxins such as cadmium. Additionally, the relationship between early markers of renal tubular dysfunction, such as the urinary excretion of low molecular weight proteins or *N*-acetyl β-D-glucosaminidase (NAG) to subsequent development of renal failure, remains to be determined (*46*).

Chronic exposure to high concentrations of lead results in a high incidence of chronic nephropathy (*10,47–49*). In general, individuals with blood lead levels exceeding 60 µg/dl (2.89 µmol/l) are at a definite risk of developing renal failure (*45,50*). More recently, it has become evident that blood lead levels as low as 10 µg/dl (0.48 µmol/l), previously considered to be safe, may also be associated with renal functional abnormalities. In a recent study, Staessen et al. (*51*) determined renal function and indices of lead exposure in a random population sample from Belgium, including 965 men and 1,016 women. The creatinine clearance was inversely correlated with blood lead and zinc protoporphyrin concentrations in both men and women (Fig. 2). There was also a positive correlation between serum β_2-microglobulin and blood lead levels in men. The same authors had previously found only

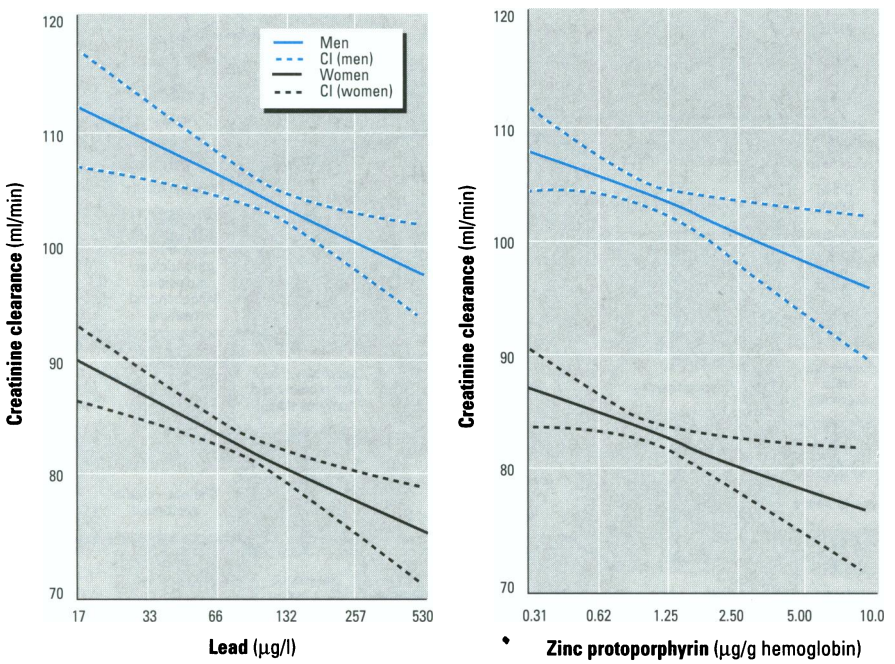

Figure 2. Relationship between measured creatinine and blood lead and zinc protoporphyrin levels, adjusted for age, body mass index, and diuretic use. Regression lines and 95% confidence intervals (CI) are shown separately for men (n = 965) and women (n = 1,016). Reproduced from Staessen et al. (*51*) with permission from the *New England Journal of Medicine*.

a weak positive correlation between serum creatinine and blood lead concentrations in a study conducted in London civil servants (*52*). More recently, Kim et al. (*53*) reported the results of a longitudinal study of 459 men followed for 35 years, as part of a study of aging. They found a positive correlation between blood lead levels and serum creatinine concentrations. A 10-fold increase in blood lead level predicted an increase of 7 µmol/l (0.08 mg/dl) in serum creatinine concentration. Whether such small changes in renal function will result in clinically significant health problems is uncertain and will require even longer studies.

Lead nephropathy due to occupational lead exposure. A multitude of studies have documented an association between chronic occupational lead exposure and impairment of renal function (*22,23,48,49,54*). Additionally, there appears to be an excess risk of mortality from renal disease with increasing duration of lead exposure (*55–58*). Wedeen et al. (*14*) studied eight subjects with occupational lead exposure of 3–6 years duration and found renal functional abnormalities in four individuals. Renal function improved with chelation therapy in one subject reported to have preclinical renal failure. The authors found no changes in the tubular reabsorption of phosphate or of sodium in their patients, but noted proximal tubular abnormalities on renal biopsy in three patients who had decreased GFR. Baker et al. (*48*) evaluated 160 lead workers in two smelters and a chemical plant. Increased blood urea nitrogen (BUN; >20 mg/dl, 7.14 mmol/l) was found in 28. Eight workers had reduced creatinine clearance. Lilis et al. (*50*) studied 449 lead workers with different levels of lead exposure [from <40 to >100 µg/dl (<1.93 to >4.83 µmol/l)], and found highly significant correlations between BUN and creatinine and zinc protoporphyrin levels. Hong et al. (*54*) investigated the tubular and glomerular function of six adults with occupational exposure to lead. Lead exposure had ranged from 3 months to 22 years, and all subjects had elevated blood lead levels [>30 µg/dl (>1.45 µmol/l)]. Serum creatinine and BUN were normal in all subjects. Urinary excretion of β_2 microglobulin was also found to be normal in all. However, glucose reabsorptive capacity (Tm_G) was decreased in all subjects. The presence of glycosuria without increased excretion of low molecular weight proteins suggests a selective effect of lead on the proximal tubular glucose transporter protein.

Several studies have used a control group to assess the effect of lead exposure on renal function. Two studies involving heavily exposed individuals have shown a positive association between lead and renal impairment: Pinto de Almeida et al. (*49*) compared the renal function of 52 primary lead smelter workers [mean PbB 64.1 µg/dl (3.1 µmol/l) with those of 44 control workers [mean PbB 25.5 µg/dl (1.23 µmol/l)]. Seventeen lead workers had a serum creatinine ≥1.5 mg/dl (132.6 µmol/l), compared to only one control individual. Verschoor et al. (*59*) compared the renal function of 155 lead workers to those of 126 control workers. The mean blood lead level in exposed workers was 2.29 µmol/l (47.4 µg/dl). Several parameters of renal tubular function were evaluated and found to be affected by lead. Serum β_2-microglobulin decreased and urinary excretion of retinol binding protein increased with increasing blood lead level. Urinary excretion of NAG increased with increasing blood lead and zinc protoporphyrin concentrations. The increased urinary NAG appeared to be the most consistent change.

A somewhat less clear relationship between lead and renal dysfunction has been found in individuals with less severe occupational exposure: Gerhardsson et al. (*60*) studied 70 active and 30 retired lead smelter workers and compared their renal function to that of 41 workers who had not been exposed to lead. The median lead level for lead-exposed workers was 1.54 µmol/l (32 µg/dl). No clinical signs of renal impairment were found, including no relationship between urinary NAG and blood lead concentrations. Greenberg et al. (*61*) studied 38 industrial workers exposed to lead and cadmium for 11–37 years and found normal creatinine clearances in all, despite a documented increase in lead burden in 36–58% of the subjects. The lower blood lead concentrations of these workers, compared to those studied by Pinto de Almeida et al. (*49*) or by Verschoor et al. (*59*), may explain some of the negative findings.

Chia et al. (*62*) studied renal functional parameters in 137 lead-exposed workers [PbB <60 µg/dl (<2.89 µmol/l)] and in 153 control postal workers. The mean creatinine clearances were not different between the two groups. Only 8 subjects with lead exposure had decreased creatinine clearance. Serum β_2-microglobulin was lower in lead-exposed subjects, particularly in those over 30 years of age. Buchet et al. (*63*) conducted a study of lead-exposed workers employed for a mean of 13.2 years and having a moderate exposure to lead resulting in blood lead levels <62 µg/dl (<2.99 µmol/l). They were unable to show any effect of lead on renal function. Similarly, Omae et al. (*64*) performed a cross-sectional study of 165 lead-exposed men with a mean blood lead level of 36.5 µg/dl (1.76 µmol/l) and found no change in serum creatinine or in the urinary clearance of β_2 microglobulin or uric acid. These three studies appear to confirm the previously reported observation that renal failure is seldom observed when blood lead levels remain below a critical threshold of 60 µg/dl (2.89 µmol/l).

In summary, the preponderance of studies suggests that occupational exposure to lead results in renal functional abnormalities, ranging from proximal tubular dysfunction to chronic renal failure and hypertension. Three studies show no change in renal functional parameters and one shows abnormal urinary concentrating ability (Table 1). In general, longer exposure and higher blood lead levels appear to be common features among individuals who develop lead nephropathy.

Does childhood lead poisoning result in lead nephropathy? Chronic nephropathy in young adults following untreated lead poisoning in childhood was first described in 1929 from Queensland, Australia, by Nye (*10*). The mode of exposure to lead was somewhat unique among these children. While playing on the verandas of wooden houses typical of this region, the children had ingested leaded paint debris and licked the sweet-tasting lead-containing rain water collected on the railings. In 1954, Henderson (*11*) studied 401 individuals who had been diagnosed as having lead poisoning between 1915 and 1935. Of these, 165 had died, 108 from nephritis or hypertension, an incidence which far exceeded that in the rest of Australia. The characteristic clinical presentation included granular contracted kidneys, hypertension, renal failure, and, in half of the cases, hyperuricemia and gout (*44,65,66*). In additional articles, Henderson and Inglis (*67*) showed that the lead content of bone in subjects between 20 and 49 years of age who were born in Queensland and died of granular contracted kidneys were significantly higher than in subjects without such renal disease. In 1963, Emmerson (*68*) showed that lead excretion, following EDTA infusion, was consistently elevated in patients with chronic renal disease and a history of childhood lead poisoning, but not in those with renal disease due to other causes. Such observations appear to be confined to Queensland and have not been reported from other parts of the world.

Tepper (*69*) reported a follow-up study of individuals from Boston, Massachusetts, 20–35 years after childhood lead poisoning. Of 165 original cases, 139 were traced and 42 were screened with renal function tests. Only 6 were found to have mild renal dysfunction. Similarly, in a study involving 62 adolescents from Baltimore, Maryland, 11–16 years after childhood lead poisoning, Chisolm (*70*) found no evidence of excessive mobilizable lead and no evidence of nephropathy. Moel and Sachs (*71*) studied 62 subjects with severe childhood lead poisoning [PbB >100 µg/dl (>4.83 µmol/l)] along with 19 age-matched control siblings [PbB <40 µg/dl (<1.93 µmol/l)] from Chicago, Illinois, 17–23 years after the children had undergone chelation therapy. They found no difference between the study subjects and controls in any of the parameters studied, including serum creatinine, urinary excretion of β_2 microglobulin, and systolic or diastolic blood pressure. This led the authors to conclude that lead nephropathy is not a common sequela of childhood lead poisoning in the United States. In none of the above studies, however, did the investigators use recently available and more sensitive tests of tubular function such as urinary excretion of NAG or brush border enzymes. Therefore, subtle changes in renal tubular function may have been missed. Chisolm (*70*) has suggested that the lead toxicity in the Queensland population was of a different type and had a more protracted course than that observed in the United States.

A more recent retrospective study was conducted in Boston, which compared the renal function of individuals 50 years after childhood lead poisoning with those of carefully matched controls (*72*). The authors found no evidence of impaired renal function, as assessed by measurement of glomerular filtration rate. In fact, the mean creatinine clearance of subjects with a past history of plumbism was higher than that of controls. The authors, however, noted a higher incidence of hypertension among subjects with past lead poisoning compared with controls (*72*).

Several recent studies suggest a relationship between childhood lead exposure and subsequent impairment of renal function. In a cross-sectional study of lead and kidney function in 744 men from Boston [mean PbB 8.1 ± 3.9 µg/dl, (0.39 ± 0.19 µmol/l)], Payton et al. (*73*) found a significant negative correlation between creatinine clearance and blood lead levels. Bernard et al. (*19*) studied the renal tubular function of 144 children, 12–15 years of age, recruited from two schools in the vicinity of a lead smelter and 51 children of similar age from a school in a rural area. Children from the polluted areas had higher urinary excretion of retinol binding protein, which paralleled the levels of lead in blood and in the dust gathered from the children's schools. Serum creatinine levels, however, were not different between groups. Verberk et al. (*74*) evaluated 151 children residing at various distances from a lead smelter. They found a relationship between blood lead concentration and the activity of NAG in urine, suggesting renal tubular damage due to lead (Fig. 3). They failed, however, to find changes in retinol binding protein. In a recent epidemiologic study of 454 individuals with a diagnosis of childhood lead poisoning between 1923 and 1966, there was an increased mortality from cardiovascular disease and cerebrovascular disease compared to the general population, especially among women (*75*). Chronic nephritis, however, was not a significant cause of death in this population.

Although a common occurrence in acute lead poisoning, renal tubular transport abnormalities have rarely been reported in patients with chronic lead nephropathy, whether from Queensland or in patients with occupational lead exposure. Hong et al. (*54*) reported a reduction in renal tubular glucose reabsorption in lead workers with otherwise normal renal function, as assessed by serum creatinine concentrations. Buchet et al. (*63*) studied 25 lead-exposed workers with blood lead levels below 62 µg/dl (2.99 µmol/l). There were significant positive correlations between urinary lead excretion and urinary amino acids ($r = 0.595$) and urinary lactate dehydrogenase ($r = 0.407$) excretion. There were no changes in serum creatinine or in creatinine clearance in these subjects.

In a retrospective study of 134 children and adolescents 8–13 years after treatment for severe lead poisoning, we found subtle changes in renal tubular function (M. Loghman-Adham, unpublished data). At the time of the study, the mean blood lead level was 18.5 µg/dl (0.89 µmol/l). Creatinine clearance was normal (>80 ml/min/1.73 M^2) in all but three children. Thirty-two children (24%) continued to have glycosuria (>124.8 mg/24 hr) and 94 (70%) had persistent aminoaciduria ($U_{aan}/Cr > 0.23$).

In summary, sustained environmental lead exposure, particularly during childhood, can under certain circumstances result in chronic lead nephropathy. Three studies from the United States have failed to show any evidence of nephropathy in individuals who had been treated for childhood lead poisoning. One study, while confirming the absence of chronic nephropathy, shows persistent tubular dysfunction, manifested by glycosuria and aminoaciduria. Among four large epidemiologic studies of children with increased lead exposure, three studies found evidence of renal tubular dysfunction. None, however, found any evidence of nephritis or reduced glomerular filtration.

Lead nephropathy in "moonshine" drinkers. A high incidence of chronic lead nephropathy has been described in "moonshine" drinkers, those who drink illegally distilled whiskey. Typically these individuals have also been reported to suffer from hypertension and hyperuricemia with gout (*13,14,53,76,77*). This illegal whiskey has commonly been distilled in rural areas in the Southeastern United States. The alcohol is often brewed in galvanized tubs and distilled in truck radiators. Lead battery plates, moth

Table 1. Summary of studies of the effect of lead on renal function

Exposure type	Description of subjects	Duration of exposure	Blood lead levels
E	80 subjects from Queensland, Australia	Unknown	Not done
E	401 children diagnosed with Pb poisoning between 1915 and 1935	19–39 years	Not done
E	81 members of 12 families exposed to lead-contaminated flour	Unknown	>100 µg/dl
E	139 of 165 original cases ascertained, tests in 42	20–35 years	Unknown
E	62 adolescents	11–16 years	Unknown
E	283 subjects drinking water with lead concentrations >100 µg/l	≥21.5 years	<1.5–>4.5 µmol/l
E	62 subjects lead-poisoned in childhood, and 19 sibling controls	17–23 years	Initial: 150.3 ± 77 µg/dl; current: 7.4 ± 0.1 µg/dl
E	965 men and 1,016 women age 20–88 years	Unknown	Men, 11.4 (23–72.5) µg/dl; women, 7.5 (1.7–60.3) µg/dl
E	123 subjects living at various distances from a lead battery factory	>10 years	7.48–16.63 µg/dl
E	744 men	Unknown	8.1 ± 3.9 µg/dl
E	144 children near a lead smelter and 51 children from a rural area	Unknown	Mean Pb levels (µg/dl), control, 8.39–8.7; exposed, 9.44–14.9
E	459 men	Unknown	0.48 ± 0.30 µmol/l (9.9 ± 6.1 µg/dl)
E	151 children living at different distances from a lead smelter	Unknown	Control, 15.5 ± 3.7 µg/dl; exposed, 43.8 ± 14.8 µg/dl
O	53 subjects (average age 33.9 years)	2 months–35 years	PbB >60 µ/dl in 42 subjects
O	102 subjects 32–61 years of age	7–41 years	PbB 42–141 µg/dl
O	8 subjects, 28–50 years of age	3–6 years	PbB 52.6 ± 21.4 µg/dl
O	160 lead-workers, 29–62 years of age	4.5–31 years	0.77–13.51 µmol/l (16–280 µg/dl)
O	449 subjects with different levels of occupational lead exposure	Average exposure up to 12 years	>80 µg/dl in 59% of subjects from a secondary lead smelter
O	25 lead-exposed workers and 88 control workers	Unknown	<62 µg/dl
O	6 adults, 22–54 years of age	3 months–22 years	PbB 68.3 ± 24.9 µg/dl
O	38 workers exposed to lead and cadmium. Increased Pb burden in 58%, increased Cd burden in 31%	11–37 years	PbB 32 ± 14 µg/dl (range 9–60)
O	52 workers from a lead smelter and 44 controls from a paper mill	Unknown	Exposed, 64.1 ± 16.3 µg/dl; controls, 25.5 ± 4.4 µg/dl
O	155 lead workers and 126 control workers	Unknown	Exposed, 2.29 µmol/l (mean); control, 0.40 µmol/l (mean)
O	165 lead-exposed workers	0.1–26.3 yrs	Mean, 36.5 µg/dl; range, 9–60 µg/dl
O	70 active and 30 retired lead workers, 31 active and 10 retired truck assembly workers	Unknown	Median Pb levels: active, 1.54; retired, 0.48 µmol/l; control, 0.17–0.2 µmol/l
O	50 lead-exposed subjects and 50 controls	14 years (average)	Exposed 48 (range 36.3–64.6) µg/dl; control, 16.7 (range 6.3–34.3) µg/dl
O	82 lead battery workers and 44 healthy volunteers	7 years	Exposed, 2.03 (range 1.01–3.53) µmol/l; control, 0.34 (range 0.24–0.53) µmol/l
O	160 lead-exposed workers and 60 control workers	4.5 years (median)	Median Pb level, 36.8 µg/dl
O	81 lead-exposed men and 45 age-matched controls	7 years	Exposed, 2.03 (range 1.01–3.53) µmol/l; control, 0.34 (range 0.24–0.53) µmol/l
O	128 lead-exposed workers and 152 controls (average age 27–28 years)	Unknown	Exposed, 29.6 µg/dl (mean); control, 8.7 µg/dl (mean)
O	128 Pb workers (17–52 years of age) and 93 controls (16–44 years of age)	Unknown	Exposed, 32.6 µg/dl; control, 9.0 µg/dl
O	137 lead-exposed workers (16.9–51.6 years of age) and 153 control postal workers (19–54.9 years of age)	Up to 12 yrs	PbB >60 µg/dl
O	22 mechanics (20–45 years of age) and 27 controls (22–45 years of age)	Unknown	Exposed, 24.3–62.4 µg/dl; control, 19.4–30.6 µg/dl

Abbreviations: E, environmental; O, occupational; CRF, chronic renal failure; PbB: blood lead level; C_{Cr}: creatinine clearance; NAG: *N*-acetyl β-D-glucosaminidase; ZPP, zinc protoporphyrin; BUN, blood urea nitrogen; HTN, hypertension; LDH, lactate dehydrogenase; Tm_{glu}, tubular maxima for glucose.

balls, or drain cleaner are sometimes added to the mash to accelerate fermentation or to add flavor (*13*). Morgan et al. (*13*) studied 11 patients, between 34 and 50 years of age, who had lead poisoning and a history of past or present consumption of illicit alcohol. Two additional patients with a history of occupational lead exposure were also included. All had confirmatory evidence of excessive lead accumulation, as determined by the EDTA lead mobilization test. However, blood lead levels were not given, thus making it difficult to assess recent lead exposure. Renal function was impaired in all but one patient with an average serum creatinine of 2 ± 0.7 mg/dl (range 1.2–3.8 mg/dl) [176.8 ± 62 µmol/l, (range 106–336 µmol/l)]. Six of 13 patients had proven gout. Renal biopsy showed interstitial fibrosis, obsolescent glomeruli, arterial and arteriolar changes, and the presence of eosinophilic inclusion bodies in many tubular cells. These patients appear to represent cases with severe acute and chronic lead poisoning and significant kidney damage. Other toxic substances present in the brews may have contributed to their overall toxicity.

Other Symptoms of Chronic Lead Toxicity

Lead in hyperuricemia and gout. The association between lead poisoning and hyperuricemia and gout was described as early as 1703 (*78*). In 1859, Garrod observed the relationship between the ingestion of fortified ports, later shown to be heavily contaminated with lead, and the development of gouty arthritis (*79,80*). With the popularity of leaded port wine, gout was a common occurrence among English aristocracy during

Results/comments	Reference
35 dead, 14 treated for lead poisoning in childhood	(10)
187 alive, 101 studied (17/101 with HTN and albuminuria, 3/101 with HTN only)	(11)
37/81 dead, 44/81 alive (23 with nephritis and 20 with HTN)	(47)
Average C_{Cr} = 117 ± 20; CRF in only one subject	(69)
EDTA mobilization test negative, no evidence of nephropathy	(70)
57 with urea >40 mg/dl (606 mmol/l), 20 with serum uric acid >7.1 mg/dl (0.42 µmol/l)	(20)
No difference in renal function or β_2 microglobulin excretion compared to controls	(71)
Inverse correlation between C_{Cr} and PbB or ZPP levels	(51)
Higher prevalence of NAG excretion in lead-exposed groups compared to controls	(140)
Inverse correlation between C_{Cr} and PbB	(73)
Increased urinary retinol binding protein in children from polluted areas	(19)
Positive correlation between PbB and serum creatinine	(53)
Positive correlation between PbB and NAG in urine	(74)
2 with chronic nephropathy, 8 with high BUN, 3 with HTN	(144)
17 with renal failure (most with >10 year exposure) 13 with HTN	(103)
1 with asymptomatic renal failure, 3 with preclinical renal failure	(14)
Increased BUN in 28 (most with >4 years exposure), decreased C_{Cr} in 8	(48)
BUN and Cr positively correlated with duration of exposure	(50)
Correlation between aminoaciduria and LDH in urine with lead excretion, coexposure to Cd	(63)
BUN and Cr normal in all Tm_{glu} decreased in all	(54)
C_{Cr} normal in all, 52% with abnormal urine concentration ability; 22% with hypercalciuria	(61)
Serum Cr >1.5 mg/dl in 17/52 Pb-exposed and 1/44 controls	(49)
Weak correlation between PbB and urine β_2 microglobulin or NAG (significant for workers with PbB >3 µmol/l)	(59)
No change in C_{Cr}, β_2 microglobulin or uric acid clearance; No difference for <10 year or >10 year Pb exposure	(64)
No difference in urine NAG or β_2 microglobulin between Pb-exposed and controls	(60)
Decreased urine 6-keto $PGF_{1\alpha}$, no correlation between urine NAG and PbB	(113)
Increased excretion of α_1 microglobulin and NAG in 30% of lead workers	(142)
Urine NAG higher in Pb group, correlation between NAG and duration of exposure	(94)
Increased excretion of proximal tubule markers in lead-exposed workers	(141)
Weak correlation between urine NAG and PbB. Best correlation with acute increase in PbB concentrations	(138)
Urine α_1 microglobulin higher in exposed group	(143)
Serum β_2 microglobulin more often abnormal in Pb-exposed, 8 subjects had low C_{Cr}	(62)
Correlation between PbB and NAG, higher NAG in exposed group, no correlation with β_2 microglobulin	(139)

the nineteenth century (*78*). Emmerson (*68*) investigated a group of patients with renal insufficiency in whom the nature of renal disease was not readily apparent. Evidence of excessive past lead absorption was demonstrated in 16 patients with the use of the EDTA lead mobilization test. Gout was found in half of the patients with chronic lead nephropathy but was infrequent in patients with chronic nephropathy due to other causes. About half of the patients with saturnine or lead-induced gout were female, a much higher frequency of females than that observed for gout in general. Campbell et al. (*20*) studied 283 individuals from Scotland, who lived for an average of 21.5 years in houses with water lead levels in excess of 100 µg/l (0.48 µmol/l). Fifteen subjects had increased serum urea and 20 subjects had hyperuricemia.

In the Southeastern United States, consumption of "moonshine" whiskey, known to be adulterated with lead, has been associated with a high incidence of hypertension, hyperuricemia, and gout (*13,81,82*). Although hyperuricemia is seen in chronic renal failure, the incidence of gout is much higher in chronic lead nephropathy than in other types of renal failure (*28,83,84*). In patients with lead nephropathy, there is no evidence of overproduction of uric acid, suggesting that lead may impair the renal tubular secretion of uric acid (*65,82,85*). To determine the relationship between lead and gout nephropathy, Batuman et al. (*86*) examined the body lead burden of 44 men with gout, without previous symptoms of lead poisoning, using the EDTA lead mobilization test. Among them, half had chronic

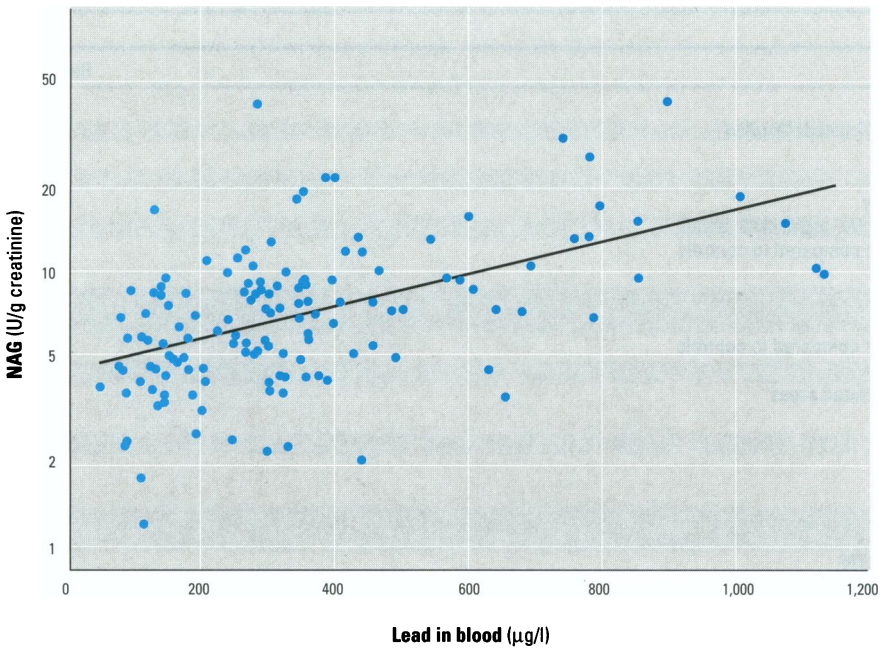

Figure 3. Relationship between blood lead levels and urinary excretion of *N*-acetyl β-D-glucosaminidase (NAG) adjusted to age 5 years in 151 children of 3–6 years of age residing in the proximity of a lead smelter. Values of NAG/g creatinine are plotted on a log scale. Reproduced from Verberk et al. (*74*) with permission from The Helen Dwight Reid Educational Foundation and *Archives of Environmental Health.*

renal disease. The amount of mobilizable lead was significantly greater in patients with gout who had renal impairment than in patients who had normal renal function. Craswell et al. (*87*) studied 44 Australian patients with chronic renal failure. Nineteen of 23 patients with gout and 8 of 19 patients without gout had positive EDTA lead mobilization tests. The authors concluded that gout, in the presence of chronic renal failure, is a useful marker of chronic lead poisoning. Long-term follow-up studies have indicated that neither hyperuricemia nor gout can lead to renal failure in the absence of other renal disease (*88*).

Lead and hypertension. There is considerable evidence that excessive lead absorption predisposes individuals to hypertension even in the absence of renal insufficiency (*89–92*). Verschoor et al. (*59*) compared the renal function of 155 lead workers [mean blood lead level 2.29 µmol/l (47.7 µg/dl)] to those of 126 control workers. Both systolic and diastolic blood pressures were higher in the lead-exposed group, with a significant correlation between blood lead levels and systolic blood pressure. De Kort et al. (*93*) compared the blood pressures of 53 workers exposed to lead and cadmium with blood pressures obtained in 52 nonexposed workers. The mean blood lead levels were 47.4 µg/dl (2.27 µmol/l) and 8.1 µg/dl (0.39 µmol/l) for the two groups, respectively. A positive correlation was found between blood lead levels and systolic blood pressure. The authors failed, however, to show any difference in kidney function between the two groups, suggesting that the mechanism of hypertension may be different from that of lead nephropathy. dos Santos et al. (*94*) studied 166 lead workers and 60 control subjects and found a higher mean diastolic blood pressure among the lead-exposed group but no difference in the systolic blood pressures between the two groups.

Exposure to lower concentrations of lead, such as via environmental sources, has also been linked to hypertension. Harlan et al. (*95*) evaluated the relationship between lead and blood pressure using data obtained during the second National Health and Nutrition Examination Survey (NHANES-II). They found a direct relationship between blood lead levels and systolic or diastolic blood pressure, regardless of the subject's sex or race. This relationship was present at blood lead levels below 30 µg/dl. Weiss et al. (*96*) studied the relationship of lead with blood pressure in a longitudinal study over 5 years in a cohort of 89 Boston policemen. They concluded that a high blood lead level was a predictor of subsequent elevation of systolic blood pressure. Wolf et al. (*97*) studied a group of 507 male law enforcement officers without occupational exposure to lead. The mean blood lead level of the subjects was 8 ± 3.5 µg/dl (0.38 ± 0.17 µmol/l). There was a significant effect of lead only on diastolic blood pressure. In a recent longitudinal study of childhood plumbism from Boston (*98*) among matched pairs of subjects, 14% of controls were on antihypertensive medications compared with 41% of individuals with childhood lead poisoning. Schwartz (*99*) has performed a meta-analysis based on 15 published papers on the effect of blood lead on systolic blood pressure in males. He evaluated the estimated change in blood pressure associated with a change in blood lead from 10 to 5 µg/dl in each study. From this careful analysis he concluded that there is a causal association between lead and blood pressure.

Animal studies have confirmed the observations made in human populations. Exposure of rats to lead during development can result in progressive renal insufficiency and hypertension later in life (*41*). Additionally, low-level lead exposure in rats causes a progressive elevation of systolic blood pressure without evidence of renal impairment (*100,101*). Dietary calcium can influence the effects of lead on blood pressure: lower dietary calcium intake is associated with higher blood pressure and decreased calcium intake can aggravate the toxic effects of lead exposure (*95,102*).

The pathogenic mechanisms for lead-induced hypertension remain unclear. Vascular changes have been shown to occur in acute lead poisoning associated with nephropathy (*103*). Lead causes increased responsiveness to α adrenergic stimulation (*104–106*), an augmented and prolonged pressor response to norepinephrine stimulation, and reduced effectiveness of isoproterenol in lowering blood pressure (*107*). These findings suggest an interaction of lead with calcium signaling mechanisms involved in smooth muscle contraction (Fig. 1) (*99,108*). Hypertension may also be the result of lead-induced changes in the vasculature, the renin–angiotensin system (*109–111*), or in renal ion transport processes (*28*). Lead has been shown to increase the *in vitro* sodium–lithium countertransport in red blood cells obtained from healthy normotensive individuals (*112*). The changes are similar to those observed in red blood cells from patients with essential hypertension. Cardenas et al. (*113*) studied more than 20 tests of renal function in 50 lead workers. The most striking effect of lead was interference with renal synthesis of eicosanoids, resulting in lower excretion of 6-keto-$PGF_{1\alpha}$. The authors speculated that the depletion of prostaglandins may enhance sodium retention and the pressor response to angiotensin II and vasopressin, changes that mimic those seen in essential hypertension.

In summary, excessive lead absorption results in hypertension, both in humans and in experimental animals, even in the absence of nephropathy. Epidemiologic

studies have shown a clear association between blood lead levels and blood pressure. The mechanisms of lead-induced hypertension include a direct effect of lead on the vasculature, increased responsiveness to α adrenergic stimulation, interference with the renin–angiotensin system, an effect on the calcium signaling mechanism involved in smooth muscle contraction, and interference with renal synthesis of vasodilatory prostaglandins and with ion transport mechanisms.

Methods to Assess Increased Body Lead Burden

Lead stored in bone has a biologic half life of approximately 30 years. Over 90–95% (70–80% in children) of body lead burden is retained in bone where it is available for exchange with blood (*114*). Blood lead levels provide a poor estimate of past lead absorption because the levels can vary with recent ingestion (*8,83,115*). Cumulative lead absorption, or body lead burden, is best evaluated by the use of the $CaNa_2EDTA$ lead mobilization test (*44,68*). The test consists of intramuscular administration of one or two doses of 1 g EDTA every 12 hr in an adult or of 50 mg/kg in a child, followed by collection of urine for 8 to 24 hr (*116*). In patients with reduced renal function, there is a delay in the excretion of lead chelate (*117*) and the collection time is extended to 72 hr. An amount of lead mobilized in excess of 600 mg (or >1 µg Pb/mg EDTA in a child) is considered proof of increased lead burden (*115*). Unfortunately, the EDTA challenge test is not a consistent predictor of body lead burden (*118*). Furthermore, the test is fraught with technical difficulties and has a potential to increase lead toxicity. Therefore, the EDTA mobilization test will probably be abandoned in the future and replaced by noninvasive tests, such as *in vivo* X-ray fluorescence (XRF), which have now become available (*119*). A drug that could be used as a possible substitute for EDTA is the water soluble and orally active chelating agent dimercaptosuccinic acid (DMSA or succimer). Limited experience suggests that DMSA does not result in increased risk of lead toxicity such as encephalopathy. Although widely used in the former Soviet Union for the treatment of heavy metal poisoning, experience with DMSA has been limited in the United States (*120,121*).

A more recent and much less invasive test for evaluation of lead burden involves the quantitation of bone lead with *in vivo* XRF (*122–132*). Measurements taken at the midtibial diaphysis using a K-XRF instrument appear to be very reliable (*125*). The lead fluorescent signal is normalized to the coherent scatter signal, which results principally from calcium in bone mineral (*125*). Using older equipment, the minimum detection limit of XRF was 25 µg/g (*123*). However, this limit has continued to decrease with improvements in technology, with a current sensitivity in the range of 5 µg/g). At present, XRF is not widely available for routine clinical use; however, since it is an accurate and noninvasive means of determining body lead burden, its use will undoubtedly become more widespread.

Tests for Detection of Kidney Damage Due to Lead

Chronic lead nephropathy can be missed in its early stages because changes induced by chronic low-level lead exposure are subtle and not reflected by changes in routine renal function tests such as BUN and serum creatinine concentrations. More than 50% of kidney function may be lost before significant changes in serum creatinine are detected. .

Recent studies have focused on the use of more sensitive tests to detect lead-induced renal dysfunction in its early stages, when such changes might still be reversible by treatment and abatement of lead sources. Currently recommended tests of nephrotoxicity include the measurement of urinary excretion of proteins, which, according to their size, reflect the functional integrity of the proximal tubule (retinol binding protein or β_2 microglobulin) or of the glomerulus (albumin, immunoglobulin G) (*133*). Although β_2 microglobulin can be degraded in acid urine, retinol binding protein is not hydrolyzed in acidic pH and therefore may be a more reliable marker. Expressing the urinary excretion of low molecular weight proteins as fractional clearance (ratio of clearance of protein over creatinine clearance) has been used to increase the sensitivity of such tests (*134*). More sensitive tests, such as determination of levels of enzymes excreted in the urine, have revealed evidence of tubular toxicity in patients with chronic low-level lead exposure, whether secondary to environmental or occupational lead sources. The most sensitive test appears to be urinary excretion of NAG (*74,135–140*). Verschoor et al. (*59*), in a study of lead workers with blood lead levels below 60 µg/dl (2.89 µmol/l), found the excretion of NAG to be the most sensitive marker of renal tubular dysfunction. There was, however, only a modest increase in urinary NAG excretion (from 3.0 to 3.7 U/mg creatinine) in workers with the highest blood lead concentrations (>3 µmol/l) compared to those with low (<1 µmol/l) blood lead.

It has been suggested that NAG might be an overly sensitive test because its levels are increased in animals with continuous low-level lead exposure at a time when no other signs of kidney damage are detectable (*42,69*). More recently, the heat-stable isoenzyme of NAG has been used as a marker of lysosomal breakdown in proximal tubular cells (*138*). Endo et al. (*136*) studied 46 lead refinery workers with long-term exposure to lead dust; they found markedly increased urinary NAG activity in workers whose blood lead levels exceeded 80 µg/dl (3.86 µmol/l). In one study in rats, ligandin appeared to be a better indicator of tubular injury because it correlated with changes in tubular morphology (*42*). No information is available on ligandin excretion in humans.

Bernard et al. (*19*) studied children recruited from two schools in the vicinity of a lead smelter, with children from a rural area used as controls. Urinary excretion of retinol binding protein was elevated in children from the polluted areas and correlated with blood lead levels. Urinary β_2 microglobulin and urinary NAG were elevated only in children from one of the polluted areas, despite similar blood lead levels between children from these areas. Cardenas et al. (*113*) used a battery of more than 20 potential indicators of renal function in 50 workers exposed to lead and in 50 control subjects. The most striking effect of lead was interference with renal synthesis of eicosanoids, resulting in lower excretion of 6-keto-$PGF_{1\alpha}$. Increased urinary NAG activity was also found in lead-exposed workers. The authors found no correlation between urinary NAG and blood lead or zinc protoporphyrin levels or the duration of lead exposure. There was, however, a positive correlation between urinary NAG and urinary cadmium excretion.

Fels et al. (*141*) studied various markers of renal proximal tubule injury in 81 male lead-exposed workers and 45 age-matched controls. The mean blood lead level of lead-exposed subjects was 2.03 µmol/l (42 µg/dl), with a mean duration of exposure of 7 years. Urinary 6-keto-$PGF_{1\alpha}$ levels were higher in lead-exposed workers, as were urinary thromboxane B_2, urinary $PGF_{2\alpha}$, and PGF_2 excretion. These findings appear to be opposite those reported above by Cardenas et al. (*113*). Intestinal alkaline phosphatase and brush border antigen (BBA) excretion were also increased in 27% and 16% of subjects, respectively. In a subsequent study of the same subjects, Pergande et al. (*142*) measured the urinary excretion of low molecular weight proteins and tubular enzymes as indicators of proximal tubular damage; they found the combination of urinary NAG and α_1 microglobulin to be useful in the early detection of lead-induced tubular changes.

Chia et al. (*143*) correlated urinary α_1 microglobulin and β_2 microglobulin in 128 lead-exposed workers with time-integrated

blood lead indices derived from serial blood lead determinations over time. There was a correlation between urinary α_1 microglobulin and time-integrated blood lead, but not with recent blood lead levels. dos Santos et al. (*94*) measured biochemical markers of kidney damage in 166 lead-exposed workers and in 60 controls. The median blood lead levels were 36.8 µg/dl (1.78 µmol/l) in exposed workers and 11.6 µg/dl (0.56 µmol/l) in controls. Urinary NAG was higher in the lead-exposed group and correlated with blood lead levels and with duration of exposure. In contrast, urinary excretion of two brush border enzymes, γ-glutamyltranspeptidase and alanine-aminopeptidase, were not increased in lead exposed workers.

In summary, conventional renal function tests are insensitive and cannot detect early signs of renal dysfunction in persons exposed to occupational or environmental lead. Measurement of urinary excretion of a panel of low molecular weight proteins and enzymes provides the most sensitive means to evaluate renal tubular dysfunction after lead exposure. These tests are, however, nonspecific and can be abnormal in persons exposed to cadmium or to other nephrotoxins. Therefore, abnormal values must be correlated with evidence of chronic lead exposure.

Summary and Conclusions

Despite significant reductions in industrial and environmental sources of lead, low-level lead exposure remains a major health problem in many countries. Children are particularly susceptible because of their exploratory activity and higher gastrointestinal absorption. Acute lead poisoning in humans and in animal models causes destruction of proximal tubular architecture with functional disturbances, including aminoaciduria, glycosuria, and phosphaturia (Fig. 1). These changes are reversible after chelation therapy. Recent observations, however, have revealed persistent aminoaciduria and glycosuria up to 13 years after treatment of lead poisoning. Chronic lead poisoning, secondary to occupational exposure or consumption of lead-contaminated illicit alcohol, may result in what has been termed lead nephropathy. The latter seems to develop when blood lead levels exceed a threshold of 60 µg/dl (2.89 µmol/l). Renal histologic changes of chronic lead nephropathy are nonspecific and include interstitial fibrosis, tubular atrophy, and glomerular sclerosis. They lead to progressive and irreversible renal failure often associated with hypertension, hyperuricemia, and gout. The development of gout appears to be a common feature of lead nephropathy and may be the result of a direct effect of lead on urate secretion. Chronic nephropathy, subsequent to childhood lead poisoning, has been reported from Queensland, Australia. However, studies from the United States have failed to show any such sequelae in children up to 35 years after childhood lead poisoning. Recent longitudinal studies, however, have shown direct correlations between blood lead levels and serum creatinine or blood lead and blood pressure. Lead-induced hypertension can occur in the absence of nephropathy. The mechanisms include vascular changes, increased sensitivity to catecholamines, and an effect of lead on the renin–angiotensin system and on calcium signaling mechanisms, resulting in enhanced vasoconstriction and hypertension (Fig. 1).

Because >90% of lead is stored in bone, blood lead levels are a poor indicator of total body lead burden. The EDTA lead mobilization test has been used extensively to document increased body lead burden, but more recently, less invasive tests such as measurements of bone lead by X-ray fluorescence have gained in popularity. Early renal tubular dysfunction, secondary to low-level lead exposure, can be evaluated with measurement of urinary excretion of low molecular weight proteins (α_1 and β_2 microglobulins, retinol binding protein) or of the lysosomal enzyme NAG, as well as by a host of other brush border proteins. It remains uncertain whether the tubular dysfunction detected by these sensitive markers is of any long-term clinical significance.

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